NIMH National Institute of Mental Health

MOOD & ANXIETY DISORDERS PROGRAM

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Research Progress Report 2003-2004

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It has been a very productive year in bipolar disorder genetic research!

Two new genetic linkage studies have identified a region on chromosome 6 that harbors a gene that contributes to bipolar disorder in some families. Genetic linkage studies are a way of mapping genes by tracking the inheritance of genetic markers in a family. Markers that are consistently inherited along with disease indicate that a gene contributing to that disease lies nearby. Previous linkage studies in bipolar disorder have implicated regions on chromosomes 1, 12, 13, 16, 18, and 22. One of the things that make these new studies so important is that they point to the same broad region of chromosome 6, even though the families studied were different. The first study looked at 300 families who volunteered for the NIMH Genetics Initiative Project, a large multi-center study that includes a center I lead at the NIMH Intramural Program. The second study, led by Dr. Carlos Pato, studied several large families from a set of islands off the coast of Portugal.

This year also saw the first confirmed genetic association finding in bipolar disorder. Genetic association studies aim to identify the actual genes that contribute to disease by studying genetic markers within genes and looking for differences between people who have the disease and those who don't. This gene, known as G72/G30, was actually first identified last year in a study of people with schizophrenia. Earlier genetic linkage studies had identified a region on chromosome 13, where G72/G30 resides. Since linkage studies of bipolar disorder had also implicated chromosome 13, scientists at the University of Chicago led by Dr. Elliot Gershon studied G72/G30 in families originally collected at the NIMH in the 1980's. They found strong statistical evidence of association between markers near G72/G30 and bipolar disorder. Afterward, our team here at NIH studied the same markers in a people with familial bipolar disorder who were diagnosed by clinicians at Johns Hopkins in the 1990's. We again found strong statistical evidence of association with bipolar disorder. Most recently, a team of scientists in Europe found evidence of association between G72/G30 and bipolar disorder in people from Germany and Poland. Right now, scientists do not know much about the biology of G72/G30, except that is makes a protein that is expressed in the brain. Our task now is to uncover the actual genetic variants in or near G72/G30 that alter its function and try to understand how this contributes to bipolar disorder.

These important advances would not have been possible without the large groups of people who took the time to volunteer for bipolar disorder genetic research at these various institutions over the past 2 decades. We hope that these discoveries will soon lead to improved diagnosis and treatment of bipolar disorder, a disease that still burdens too many people and claims too many lives.

Welcome to the latest edition of the Bipolar Genetics – Family Study News, our annual newsletter for volunteers and friends of bipolar disorder genetics research at the National Institute of Mental Health. We hope you enjoy this year's edition!

Genome Scan Finds New Gene for Bipolar Disorder on Chromosome 16q and Confirms Earlier Reports of Genes on Chromosomes 16p and 18q

Lisa Etienne-Austin, Ph.D.
Postdoctoral Fellow, NIMH

The National Institute of Mental Health Genetics Initiative for Bipolar Disorder was established in 1991. The initiative consists of 12 collaborating groups of scientists in the U.S. who are committed to identifying genes that contribute to the risk of bipolar disorder. Previous rounds of this study showed evidence of genes contributing to the risk of bipolar on several. The fourth round, just completed, consisted of 275 families. We followed the inheritance of bipolar disorder in families along with the inheritance of genetic markers whose location is known. This is known as genetic linkage analysis. The families was studied usually included several relatives affected with bipolar I (BP I), schizoaffective disorder, bipolar II (BP II), and major depressive disorder. We found evidence suggestive of genes conferring a risk of BP I and schizoaffective disorder on the long arm of chromosomes 1 and 3; BP I, II, and schizoaffective disorder on the short arm of chromosome 16; and BP I, schizoaffective disorder, BP II, and major depressive disorder on the long arm of chromosomes 5, 12, and 18. These results supported the prior findings, but also highlighted some

new locations worthy of study. While genetic linkage studies are not able to identify particular genes, they do help us to focus on specific regions on chromosomes for further investigation. Thus, we are hopeful that our efforts will lead to the identification of genes associated with the increased risk of bipolar disorder.

Gene variants on chromosome 13 potentially confer risk to bipolar disorder and schizophrenia

Sevilla Detera-Wadleigh, Ph.D.
Staff Scientist, NIMH

In recent years genetic studies have unveiled evidence for overlaps of candidate chromosomal regions involved in risk to bipolar disorder and schizophrenia, leading to the speculation that these disorders share some disease-predisposing genes.

One example of a potentially shared gene for these disorders is located on the long arm of chromosome 13 (13q), informally referred to as G72 (official designation is DAOA). Interest on 13q in schizophrenia and bipolar disorder has been prompted by findings of linkage to 13q32 from whole genome scans in schizophrenia and bipolar disorder, reported in 1998 and 1999, respectively. Supportive studies from other groups have been published subsequently. A follow-up study designed to clone the susceptibility gene detected significant overrepresentation in schizophrenics of specific variants, and combinations of these, that map to the G72 region. Results of our studies in bipolar disorder were consistent with these findings suggesting that either G72 or another gene nearby is involved in predisposition to bipolar disorder and schizophrenia. Other samples are being investigated to verify these findings. Currently, studies are being targeted on a broader portion of 13q because linkage peaks from various studies extend the region of interest, suggesting the possibility that one or more susceptibility genes map to 13q. Additional linkage reports in bipolar disorder and schizophrenia suggest similarly shared risk variants in other parts of the genome, and continued intense research efforts should lead to their identification.

Who's Who in Bipolar Disorder Genetics Research at NIMH

Francis J. McMahon, Chief. Dr. McMahon received his B.A. in Biology from the University of Pennsylvania in 1982 and his M.D. from Johns Hopkins University School of Medicine in 1987. He stayed on at Hopkins to complete a medical internship, a residency in adult psychiatry, and a post-doctoral fellowship in psychiatric genetics before joining the faculty in 1993. In 1998, he became Associate Professor of Psychiatry and medical director of the Electroconvulsive Therapy Clinic at the University of Chicago. In 2002, he joined the Mood and Anxiety Disorders Program as chief of its Genetics Unit. Dr. McMahon was named a Mallinckrodt Scholar by the Edward F. Mallinckrodt Foundation in 1999. He also serves as a scientific advisor for the National Tourette Syndrome Association, the University of Antwerp, the RIKEN Brain Science Institute, and several scientific journals. He is author or coauthor of numerous scientific reports (see p. 4) and several textbooks.

Sevilla Detera-Wadleigh, Staff Scientist. Dr. Detera-Wadleigh joined NIMH following a postdoctoral fellowship at the Laboratory of Biochemistry, NCI, NIH. She has been actively involved in research aimed at understanding the genetic basis of mood disorders, and has been examining linkage regions that have been highlighted in her study to identify susceptibility variants. As part of this project she has also cloned and studied genes that may have relevance to these diseases. She has written book chapters and published 90 publications in peer-reviewed journals. Dr. Detera-Wadleigh has directed and supervised the research of postdoctoral fellows and Ph.D. students. She is a member of the Editorial Board of two journals.

Layla Kassem, Fellow. Dr. Kassem completed her doctorate in clinical psychology in 1993. She completed her postdoctoral training in Boston and Chicago. She is currently working on two projects. The first is at NIMH/NIH at the Genetics of Mood and Anxiety Disorders Program, and the second is at the University of Chicago in the Committee on Human Development. Her interests include genetics of chronic psychiatric disorders and cultural issues in diagnosis and treatment. Her main responsibilities at NIMH include family interviews, and the analysis of clinical data. Her work at University of Chicago includes cross-cultural research on psychiatric disorders and their phenotypes as well as the interface between traditional healers and trained psychotherapists, and the evolution of the field of psychiatry in Lebanon and Egypt.

Nirmala Akula, Senior Technician. Ms. Akula has been working on the genetics and bioinformatics of bipolar disease since 2000. She manages DNA samples and genotyping, with a focus on chromosome 18. She obtained her Masters in Biology with specialization in Biotechnology from Illinois Institute of Technology, Chicago and a Masters in Computer Science from University of Chicago, Chicago.

Silvia Buervenich, Fellow. Dr. Buervenich, Ph.D., post-doctoral fellow since Oct. 2002. Attended Medical School in Heidelberg, Germany 1993 to 1996 and then became Erasmus scholar at the Karolinska Institute in Stockholm, Sweden, 1996 to 1997. She entered the Ph.D. program in Neuroscience at the Karolinska Institute in 1997, where she successfully defended her Ph.D. thesis on "Candidate Genes and the Dopamine System," in May 2002.

Lisa Etienne-Austin, Fellow. Dr. Austin is a native Washingtonian. She received her B.S. degree in Biology from the University of Maryland at Baltimore County, M.S. and Ph.D. degrees in Genetic Counseling and Genetics and Human Genetics, respectively, from Howard University. She joined the Genetics Basis of Mood and Anxiety Disorders lab in 2003. She is primarily responsible for the statistical analysis of the collected data.

Jo Steele, Senior Technician. Ms. Steele has been involved with the bipolar genetics project for about 10 years, primarily managing the large quantities of data that is generated. For the

last two years she has been at NIMH, where she prepares the laboratory and clinical data for analysis. Previously, she worked with Dr. McMahon and others at Johns Hopkins University, in Baltimore. She has a B. Eng (Hons) in Electronics from Southampton University, in the United Kingdom.

Winston R. Corona, Laboratory Manager. Mr. Corona was born in Chile and obtained a degree in Engineering in 1981 from the University of Chile in Santiago. After coming to the United States he obtained a B.S. degree in Environmental Sciences and Marine Biology in 1994 from the University of the District of Columbia. He currently is enrolled in a graduate program in Biochemistry at Georgetown University. His interest in research involving pure sciences, which began in 1984 after traveling around the Atacama Desert in the north of Chile, brought him to NIH to work as a Special Volunteer in 1999. He is co-author of two publications.

Diane Kazuba, Site Coordinator. Ms. Kazuba received her degree at the University of Maryland with a double major in Psychology and Social Work. She began working as a psychologist in the Clinical Genetics Branch at the National Institute of Mental Health (NIMH) in 1986. There she was mainly involved with genetic studies of siblings with bipolar disorder and schizophrenia. In June of 1998 she transferred to the Adult Obsessive-Compulsive Disorder (OCD) research unit at NIMH, where she remains involved in family studies of OCD and bipolar disorder. She is responsible for recruitment and enrollment of study volunteers and conducts structured clinical interviews with patients and their family members.

Victor A. Lopez, Visiting Fellow. Dr. Lopez was born in Guatemala where he obtained his MD degree from the University of San Carlos de Guatemala in 1995. He completed his residency in Psychiatry in the National Hospital of Mental Health of Guatemala in 2000. He has been working on the genetics of Bipolar disorder since, 2002. With the support of the Pan American Health Organization, he came to the NIH as post-doctoral fellow in Sept. 2003. Currently, he is studying clinical features of bipolar disorder in families.

Erin Snyder, Research Assistant. Erin Snyder has been working as a research assistant with the bipolar disorder family studies at the National Institute of Mental Health since 2003. She is involved with the clinical aspects of the study, including scheduling and enrolling study volunteers, interviewing participants, and working with the clinical data. In 2002, she graduated from the University of Maryland at College Park with a degree in psychology. She hopes to begin graduate school next year to further her studies in psychology, while continuing her work on this project.

Juliet J. Guroff, Clinical Research Coordinator.
Julie Guroff joined the NIMH intramural program in 1977, in the research unit that became the Clinical Neurogenetics Branch. She developed that group's original data collection and management system for psychiatric genetics, handling both clinical and molecular data. After earning her Master's degree in Social Work from the University of Maryland, she participated in developing the first NIMH Genetics Initiative interview form for family genetic research, and conducted clinical interviews with bipolar disorder patients and their family members. In 1998 she moved to the Adult Obsessive-Compulsive Disorder research unit, now combined with the Mood and Anxiety Disorders Program. She works with clinical research volunteers in family studies of OCD and bipolar disorder, coordinating their donations of clinical samples for genetic analysis.

Web Sites of Interest

NIMH Bipolar Genetics Initiative - http://www.bipolargenes.org
NIMH Neurosciences research - http://neuroscience.nih.gov

... about bipolar illness and clinical studies:
National Institute of Mental Health - http://www.nimh.nih.gov
NIMH-sponsored Clinical Trials - http://www.nimh.nih.gov/studies/index.cfm
National Library of Medicine's Clinical Trials Database - http://clinicalstudies.info.nih.gov
NIMH Publication Order Form - http://infocenter.nimh.nih.gov/index.cfm

... support groups:
National Alliance for the Mentally Ill - http://www.nami.org
Depression and Bipolar Support Alliance (formerly
National Depressive & Manic Depressive Association) - http://www.dbsalliance.org

Questions, Comments? Please contact us at:

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For your interest…further reading on the genetics of bipolar disorder

Dick DM, Foroud T, Flury L, et al. "Genomewide linkage analyses of bipolar disorder: A new sample of 250 pedigrees from the National Institute of Mental Health Genetics Initiative". *American Journal of Human Genetics*. 2003 73:107-144

Schulze TG, Buervenich S, Badner JA, et al. "Loci on chromosomes 6q and 6p interact to increase susceptibility to bipolar affective disorder in the National Institute of Mental Health Genetics Initiative pedigrees". *Biological Psychiatry*. 2004 56:18-23.

Schulze TG & McMahon FJ. "Genetic linkage and association studies in bipolar affective disorder: A time for optimism". *American Journal of Medical Genetics*. 2003 123C:36-47

Hattori E, Liu C, Badner JA, et al. "Polymorphisms at the G72/G30 gene locus, on 13q33, are associated with bipolar disorder in two independent pedigree series". *American Journal of Human Genetics*. 2003 72:1131-40

Belmaker RH. "Bipolar disorder". *New England Journal of Medicine*. 2004 351:476-86.

Middleton FA, Pato MT, Gentile KL, et al. "Genomewide linkage analysis of bipolar disorder by use of a high-density single-nucleotide-polymorphism (SNP) genotyping assay: a comparison with microsatellite marker assays and finding of significant linkage to chromosome 6q22". *American Journal of Human Genetics*. 2004 74:886-97.

DePaulo JR Jr. "Genetics of bipolar disorder: where do we stand?" *American Journal of Psychiatry*. 2004 161:595-7.